

Amendments

The specification has been amended to delete "an embolizing" prior to "composition" at page 6, line 4, which renders this section of the specification consistent with now presented Claim 1. Entry of this amendment is earnestly solicited.

Rejection Under 35 U.S.C. §103

Claims 1-15 stand rejected under 35 U.S.C. §103 over Tanabe, U.S. Patent No. 5,443,454, in view of Taki, Medical Tribune, pp. 46-47, October 26, 1989; Leshchiner, et al., U.S. Patent No. 4,795,741, Okada, et al., U.S. Patent No. 5,202,352, and Winchell, U.S. Patent No. 4,079,124. For the following reasons, this rejection is traversed.

Applicants' Invention

The claimed invention is directed to Applicants' discovery of a novel injectable liquid embolizing composition comprising an ethylene vinyl alcohol copolymer dissolved in a biocompatible solvent and a water insoluble contrast agent selected from either tantalum, tantalum oxide, or barium sulfate. The compositions of this invention are particularly suited for embolization of blood vessel and, surprisingly, these compositions are easily delivered to the vascular site and rapidly form a coherent solid material which encapsulates or entraps the water insoluble contrast agent.

The feature of forming a coherent solid material upon contact with the aqueous blood medium is an essential feature of this invention particularly as it relates to the ability of the composition to embolize blood vessels. Simply put, a non-coherent mass formed in the blood vessels will not provide the necessary degree of repeatable embolization to be clinically useful.

In the present case, entrapment of the water insoluble contrast agent within the polymer precipitate apparently is essential to the formation of a suitable coherent

precipitate upon contact with an aqueous environment as evidenced by Example 3 of this application. Specifically, in this example, compositions of this invention were compared against similar compositions employing a water soluble contrast agent. The results of this example illustrate the quality of the precipitate formed in *in vitro* experiments by injecting into an aqueous solution a composition containing ethylene vinyl alcohol copolymer (EVOH), dimethylsulfoxide (DMSO) and either a water soluble contrast agent or a water insoluble contrast agent of this invention. In the case of the water insoluble tantalum sample, a precipitate immediately formed which was characterized by firm spongy filaments and nodules. The water soluble metrizamide sample on the other hand did not form a well defined solid mass as the metrizamide rapidly diffused away.

Notwithstanding statements to the contrary in the Office Action¹, Applicants maintain that the results of their Example 3 demonstrate that the compositions of this invention possess surprising and unobvious results over compositions containing a water soluble contrast agent.

In view of the above, the claimed invention is directed to both compositions comprising the combination of EVOH/DMSO and a water insoluble contrast agent which compositions provide, as above, enhanced precipitates when added to an aqueous solution as compared to similar compositions employing a water soluble contrast agent. The claimed invention is also directed to methods for embolizing blood vessels where the characteristics of the polymer precipitate formed in the blood vessel is critical to its effectiveness in embolizing that vessel.

Returning back to the rejection, the test for non-obviousness articulated by the Court of Appeals for the Federal Circuit in *In re Sernaker* is a two-part analysis based on the prior art which seeks to determine:

¹ The Office Action states starting at the last two lines of page 3 that Applicants have failed to provide any evidence of unexpected results.

- (a) whether a combination of the teachings of all or any of the references would have suggested (expressly or by implication) the possibility of achieving further improvement by combining such teachings along the line of the invention in suit, and
- (b) whether the claimed invention achieved more than a combination which any or all of the prior art references suggested, expressly or by reasonable implication.

In re Sernaker, 702 F.2d at 994, 217 U.S.P.Q. 1, at 5 (Fed. Cir. 1983).

The first part of the test goes to the question of motivation, and refers to a well established holding from earlier case law that there must be some logical reason at the time of the invention for combining the references along the lines of the invention; otherwise the use of the teachings as evidence of non-obviousness will entail prohibited hindsight. *Ex parte Stauber and Eberle*, 208 U.S.P.Q. 945, 946 (Bd. App. 1980). The second part of the test covers another well-established basis for demonstrating non-obviousness--surprising and unexpected results.

Application of the test set forth by *In re Sernaker*, supra, to the references cited in the Office Action demonstrate that none of the cited references, either alone or in combination, suggest the benefits achieved by the claimed compositions and methods and therefore these references fail to satisfy the second part of the Sernaker test. Specifically, while the cited Tanabe reference does, in fact, recite the use of EVOH polymers in DMSO compositions for use in embolizing blood vessels, this reference only merely suggests the use of contrast agents in combination therewith without regard to the type of contrast agent. Accordingly, there is no disclosure in Tanabe of water insoluble contrast agents as per this invention nor is there any suggestion that the water insoluble contrast agents would provide benefits in the quality of the precipitate formed over conventional water soluble contrast agents as were heretofore employed in combination with EVOH/DMSO.² In point of fact, Tanabe would suggest equivalence of both water

² See, for example, Taki, et al., *American Society of Neuroradiology*, 11:163-168 (1990), cited at the first page of the specification.

insoluble and water soluble contrast agents in combination with EVOH. However, the data of Example 3 of Applicants' specification shows otherwise.

As to the cited secondary references, the cited Taki reference does not disclose the polymer composition employed in the embolization let alone the contrast agent or the solvent. The Leshchiner et al. reference teaches radio-opaque agents such as tantalum and barium sulfate *in combination with* a hyaluronan or hylan cross-linked gel. There is no teaching in Leshchiner et al. of use of these agents in combination with EVOH and Leshchiner et al. does not disclose a biocompatible solvent³ as per this invention. Rather Leshchiner et al.'s examples use water in combination with these cross-linked gels. The Winchell reference is directed to orally ingested compositions containing contrast agents which are used, e.g., in the X-ray analysis of the upper gastrointestinal tract. There is, however, no teaching in Winchell of using such contrast agents in combination with EVOH or DMSO. Lastly, the fact that Okada et al. disclose the surfactant properties of polyvinyl alcohol compounds is of no bearing to the claimed invention because such surfactant properties are not germane to the issue of precipitation. In any event, the compositions of this invention are copolymers of ethylene and vinyl alcohol and, as such, are distinguished from polyvinyl alcohol described by Okada, et al.

In view of the above, it is apparent that none of the cited references, either alone or in combination, suggest that the use of a water insoluble contrast agent in combination with EVOH and DMSO would provide for the benefits achieved in the precipitation of these compositions over similar compositions containing a water soluble contrast agents. Applicants maintain that these results are surprising and have particularly applicability to the embolization of blood vessels. Applicants submit that these results rebut any *prima facie* case of obviousness raised above and that the rejection of Claims 1-15 under 35 U.S.C. §103 over these references is in error. Withdrawal of this rejection is requested.

³ The biocompatible solvent of this invention is defined at page 9 to be an organic material.

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Applicants submit that this application is now in a condition for allowance. A notice to that effect is earnestly solicited.

Respectfully submitted,

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